

REMARKS

No amendments are proposed. The following remarks are in response to the office action mailed November 19, 2008 (“the office action”).

Rejection under 35 U.S.C. §103

Claims 1-14 were rejected as allegedly unpatentable over a combination of four references. Specifically, the rejection was based on Liu (Derwent ACC-NO 2002-217632 or CN 1327805, abstract) in view of Hwang et al. (U.S. Pat. No. 6,869,621; “Hwang”), Prakash et al. (U.S. Pat. Pub. No. 20040103908; “Prakash”) and Houck et al. (U.S. Pat. Pub. No. 20030130200; “Houck”). The office action states:

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Liu’s herbal formulation to include the other claimed active ingredients as taught by Hwange [sic, Hwang], Prakash and Houck within Liu’s herbal formulation whereby the above cited combined reference teaching as a whole would create the claimed herbal formulation and/or claimed method comprising of the claimed active ingredients to treat asthma in a subject in need thereof.

Applicants respectfully traverse this rejection. The claims are directed to herbal formulas that include an herbal mixture consisting of Ling Zhi, Ku Shen, and Gan Cao, and methods of using the formulas, e.g., for treating or lessening the severity of asthma, for suppressing GATA-3, or for suppressing the activation of memory Th2 cells. First of all, the differences between the cited references and Applicants’ claims are such that one would not have produced the claimed herbal formulas based on the references. Applicants disagree that a *prima facie* case of obviousness has been established. Second of all, even if one were to assume that obviousness had been established, the claimed herbal formulas provide unexpected efficacy at suppressing biological responses associated with asthma. Each of these points is discussed below.

Liu was cited because it “teaches a composition...containing Ku-Shen (i.e., sophora root) and a pharmaceutical carrier (i.e., the pharmaceutical could be water) to treat asthma (see, e.g., abstract).” The office action recognizes that Liu does not teach Ling Zhi and Gan Cao. Applicants disagree that Liu can serve as the basis for this rejection. Liu discloses a combination of eight Chinese medicinal materials. The abstract does not indicate that any one of the eight ingredients would be effective in a composition for treating asthma, or that one of the eight

ingredients could be combined with other ingredients for treating asthma. One skilled in the art of medicinal herbal formulations would not simply conclude that a single component of an eight component formulation could be used successfully for the same therapeutic purpose as the more complex formulation. Furthermore, the abstract of Liu certainly does not suggest that one take a single component of the eight component formula and combine it with other herbs to produce a therapeutic composition. The claimed compositions are not simple modifications of Liu's formula, as suggested in the office action.

The other cited references similarly fail to provide any suggestion of Applicants' three component formulas. Hwang mentions Ling Zhi and describes formulations of over 30 agents for the treatment of obesity. Although it mentions that Ling Zhi has efficacy in diverse conditions such as diseases of the digestive system, diseases of the respiratory system, and liver disease, Hwang does not teach or suggest that Ling Zhi is useful in the treatment of asthma with combination of other agents, much less a combination with two particular agents. With regard to the many conditions for which it is said to be effective, Hwang notes that at certain concentrations, "efficacy is weak while if it exceeds 1% by weight, this causes cost-push." Given that this reference is focused on highly complex compositions for treatment of obesity, and that it acknowledges limitations of Ling Zhi, it would not direct one to pick Ling Zhi in particular for preparation of a composition to treat or lessen the severity of asthma.

Likewise, Prakash does not describe or suggest any combination formulations that would be useful for treating or lessening severity of asthma. Prakash discloses cigarettes containing "[p]re-determined and definite amounts of different Herbal ingredients" (Prakash, abstract). Prakash's formulations include as many as twenty herbal ingredients, each of which is disclosed as possessing numerous therapeutic activities. The purpose of the cigarettes includes "[d]e-addiction from tobacco smoking," "help in the cure or relief from man diseases," "good aroma," and other nonspecific effects.

Finally, Houck was cited because it discloses use of corticosteroids and bronchodilators to treat asthma. Houck does not disclose herbal formulations to treat asthma, whether alone or in conjunction with a corticosteroid and/or bronchodilator.

The cited references disclose highly complex formulations for asthma, obesity, or to produce cigarettes. Each reference merely mentions a single component of Applicants' claims.

The references do not disclose or suggest that a three component herbal composition would have efficacy for a condition such as asthma, and they do not provide guidance as to particular components that should be included.

Moreover, Applicants have discovered that their three component herbal formula is unexpectedly effective at reducing clinical measures associated with asthma. Efficacy of a three herb formula as claimed, referred to as ASHMI in the Examples, is shown, e.g., in Examples 9-19, 21-24 of the present specification. These Examples demonstrate activity of the formula in reducing airway hyperresponsiveness, as measured by reduction in airway pressure time index (APTI), reducing lung inflammatory cells (e.g., bronchoalveolar lavage fluid (BALF) leukocytes), reducing collagen overproduction, and reducing expression of cytokines associated with asthma, among other effects. Data regarding single component formulas is provided in the present specification, e.g., in Example 26 and Figures 23-39.

A three component formula as claimed is more effective than a formula having only two of the components. Two component formulas are directly compared to a three component formula in Applicants' data attached herein as **Exhibit A**. Figure 1 shows the effect on airway hyperresponsiveness and numbers of bronchoalveolar lavage eosinophils of a three component formula, ASHMI, and two component formulas, each containing two of the ASHMI herbal components. Experiments were conducted in a mouse model of asthma described in the specification in Example 8. The data in Exhibit A, Figure 1, show that the three component formula was more effective at reducing each of these measures than any of the two component formulas. The three component formula was more than twice as effective at reducing airway hyperresponsiveness than a combination of Ling Zhi and Gan Cao, or a combination of Ku Shen and Gan Cao, suggesting a synergistic effect of the three component formula *in vivo*.

The effect of the three component and single component formulas on eotaxin-1 and IL-4 producing cell lines was also examined. The data are presented in Table 1 and Table 2 of Exhibit A. Notably, the IC₂₅ and IC₅₀ for each herb in the three component formula was dramatically lower than the IC₂₅ and IC₅₀ values for each herb used alone. These data indicate that Ling Zhi, Ku Shen, and Gan Cao had synergistic effects when used together in a three component formulation in these assays. Applicants' claimed compositions are unexpectedly superior to single or double component formulas.

For at least the foregoing reasons, Applicants submit that the present claims are patentable over Liu in view of Hwang, Prakash, and Houck. Withdrawal of the rejection of claims 1-14 as unpatentable over these references is respectfully requested.

Conclusion

Applicants invite the Examiner to contact the undersigned, Margo H. Furman, at (617) 248-4073 with any questions pertaining to the above-identified application in order to expedite prosecution of this case. This Response is being filed with a Petition for Extension of Time and required fee. In the event that any further extensions or fees are required, please consider this a conditional petition and authorization to charge any fees to Deposit Account No. 03-1721, referencing attorney docket no. 2005577-0009.

Respectfully submitted,

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